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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,905	HEINRICH ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-88 and 108-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-78* is/are rejected.

7)☒ Claim(s) *63,64,66,69,72,74 and 78* is/are objected to.

8)☒ Claim(s) *63-88 and 108-114* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/1/05;9/4/06;10/9/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Prior to entry of the amendments, claims 1-15 and 63-107 were pending.

(1) The amendment of 12/26/07 has been entered in full. Claims 1-14 and 89-107 are canceled. Claims 84-87 are amended. New claims 108-112 are added.

(2) The supplemental amendment of 1/28/08 has been entered in full. Claims 108, 109 and 112 are amended. New claims 113-115 are added.

Claims 63-88 and 108-114 are pending in the instant application.

Election/Restrictions

Applicants' election of Group III, claims 71-78, in the reply filed on 12/26/07 is acknowledged. Applicants did not indicate whether this election was with or without traverse, but because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As noted in the restriction requirement at pg 5, claims 63-70 link Groups III and IV; therefore linking claims 63-70 are currently under consideration with Group III.

In the 12/26/07 response, Applicants state that "claims 84-87 are amended to depend (directly or indirectly) from claims in Group IV. Applicants request that these claims be formally re-assigned to Group IV". The Examiner agrees and amended claims 84-87 are herewith re-assigned from Group V to Group IV.

Claims 79-88 (Group IV) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

In the 12/26/07 response, Applicants state, "Applicants have added new claims 108-112, drawn to transgenic non-human animals and cell from such animals. Applicants understand that the Office will assign these claims to a different Group than the Group(s) elected herewith, then withdraw these claims as directed to a non-elected Group" (pg 6). In the 1/28/07 response, Applicants state, "Applicants understand that

the Office will assign claims 108-115 to a different Group than the Group(s) elected previously, and withdraw them as directed to a non-elected Group" (pg 7). The Examiner agrees. Claims 108-112 are herewith assigned to new Group VII, drawn to transgenic animals and cells derived from said transgenic animals. Group VII does not share a special technical feature with the other groups for the reasons set forth at pg 3-5 of the 9/26/07 restriction requirement.

Claims 108-115 (Group IV) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants' election with traverse of the PDGFRA species of D842V (SEQ ID NO: 3 and 4) in the reply filed on 12/26/07 is acknowledged.

The traversal is on the ground(s) that "making such an election would render aspects of the elected invention inoperative" (pg 7). Applicants argue that "[b]y requiring that the Applicants elect only one sequence, the Office would effectively eviscerate those embodiments of the invention that are intended to concurrently detect whether a subject has any one (or more) of the several identified activating mutations". Applicants further argue that "there will be no serious burden to retain all of the PDGFRA variant sequences within the elected Group" because "the sequences are substantially similar to one another, by definition".

This is not found persuasive because election of a single species does not "eviscerate" other embodiments (species) that fall within an allowable genus claim. Instead, as indicated in the restriction requirement (mailed 9/26/07): "Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141" (pg 7). With respect to serious burden, while the sequences are substantially similar, each requires a separate sequence search within the relevant amino acid databases. Furthermore, in reference to the elected invention (Group III) each separate species requires separate consideration

for enablement with respect to association with "a biological condition", such that the species can be used for detection of the condition(s).

The requirement is still deemed proper and is therefore made FINAL.

Claims 63-78 are under consideration, as they read upon the elected species.

Claim Objections

Claims 63, 64, 66, 69, 72, 74 and 78 are objected to because of the following informalities:

(1) Claim 63 is objected to because it recites positions "the activating mutation comprises ... positions 2072 through 2107 or 2090 through 2937 of SEQ ID NO: 26" whereas the specification teaches that the activating residues are "found in positions 2072 to 2107 and 2916 to 2937" (¶296 of the published application). Therefore, the recitation of "2090" in claim 63 appears to be a typographical mistake.

(2) Claim 63 is objected to because the acronym "PDGFRA" (platelet-derived growth factor receptor alpha) should be spelled out the first time it is used in the claims.

(3) Claims 64, 74 and 78 are each objected to for the following inconsistencies between the recited "variants" and the submitted Sequence Listing:

(a) There is no "variant nucleic acid sequence" at position 2917 in SEQ ID NO: 5. Instead, SEQ ID NO: 5 has an 'a' residue at position 2917, as in the wild type sequence of SEQ ID NO: 1. This is confirmed by the alignment shown in Table 1 (pg 33).

(b) There is no "variant nucleic acid sequence" at position 2927 in SEQ ID NO: 7. Instead, SEQ ID NO: 7 has a 'c' residue at position 2927, as in the wild type sequence of SEQ ID NO: 1.

(c) There is no "variant nucleic acid sequence" at position 2975 in SEQ ID NO: 9. Instead, SEQ ID NO: 9 has an 'g' residue at position 2917, as in the wild type sequence of SEQ ID NO: 1.

(d) There is no "variant nucleic acid sequence" at position 2089 in SEQ ID NO: 11. Instead, SEQ ID NO: 11 has an 'c' residue at position 2917, as in the wild type sequence of SEQ ID NO: 1.

(e) There is no "variant nucleic acid sequence" at position 2017 in SEQ ID NO: 22. Instead, SEQ ID NO: 22 has an 'a' residue at position 2017, as in the wild type sequence of SEQ ID NO: 1.

(4) Claim 66 is objected to because the acronym "GIST" (gastrointestinal stromal tumor) should be spelled out the first time it is used in the claims.

(5) Claim 69 is objected to because the term "PDGFRA specific" is written without a hyphen as in parent claim 67 (i.e., "PDGFRA-specific"). Either usage is acceptable, but should be used consistently.

(6) Claim 72 is objected to because the term "PDGFRA-encoding" is written with a hyphen, unlike in parent claim 71 (i.e., "PDGFRA encoding"). Either usage is acceptable, but should be used consistently.

(7) Claim 74 is objected to because the word "or" should be present between parts (a) and (b).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method of detecting a gastrointestinal stromal tumor (GIST) associated with an activating PDGFRA mutation in a subject, comprising determining whether the subject has an activating mutation in PDGFRA, and wherein the activating mutation comprises a variant nucleic acid shown in position 2919 of SEQ ID NO: 3,

does not reasonably provide enablement for

a method of detecting a biological condition associated with an activating PDGFRA mutation in a subject, comprising determining whether the subject has an activating mutation in PDGFRA, and wherein the activating mutation comprises a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or 2090 through 2937 of SEQ ID NO: 26. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of detecting a biological condition associated with an "activating mutation in a subject" comprising determining whether a subject has specific PDGFRA mutations. The specification teaches that PDGFRA (aka PGGFR-α) is a "type III receptor tyrosine kinase with homology to KIT, FLT3, CSF1-R and PDGFRβ (PDGFRB)" and provides the wild type nucleic and amino acid sequences as SEQ ID NO: 1 (6633 nt) and 2 (1089 aa). The specification also provides consensus sequences for the PDGFRA mutants, including SEQ ID NO: 26 (nucleic acid) and 27 (amino acid). In SEQ ID NO: 26, each of residues 2072-2086, 2090-2107, and 2916-2937 are represented by 'n', wherein 'n' may "equal either no nucleotide (i.e., a deletion) or any nucleotide (i.e., a, t, g, or c)" (see the annotations for SEQ ID NO: 26). It is noted that this differs significantly from the range recited in claim 1, which states "one or more positions 2072 through 2107 or 2090 through 2937 of SEQ ID NO: 27", because in claim 1 the second range includes all residues between 2090 and 2937 (a total of 847 residues that can potentially be mutated).

The specification provides the following working examples related to the claimed invention. Example 1 describes "activating mutations in PDGFRA in GISTs [gastrointestinal stromal tumors]" and describes several mutations in exons 12 and 18 of PDGFRA (Table 1 and 2 on pg 33) found in GISTs. The specification teaches, "PDGFRA mutations have only been found in GISTs without any KIT mutation. Based on our studies to date, we believe that mutations of PDGFRA are found in approximately 34-35% of KIT wild-type GISTs or 3-6% of all GISTs" (pg 33). Example 17 continues this analysis, stating that "[u]sing the methods essentially as described in Example 1, three additional PDGFRA activating mutations were identified in GISTs"

(Table 3). Table 4 and 5 (page 55) summarize the results shown in Tables 1-3. The results described in these examels are supported by the results shown in the post-filine publication of Heinrich et al (2003. Science. 299: 708-710; cited on the 7/1/05 IDS). Example 2 is prophetic, predicting that "additional mutations will be identified at least in positions similar to those identified herein". Example 3 describes "Clinical Uses of PDGFRA Variants". Examples 4-9 describe techniques and methods for detecting mutant PDGFRA nucleic acids and proteins in samples. Example 10 describes "Differentiation of Individuals Homozygous versus Heterogzygous for Activating Mutation(s)", teaching that "it is believed that the activating variants described herein are the result of sporadic mutations rather than germline mutations, it may sometimes be beneficial to determine whether a subject is homozygous or heterozygous for the mutation" (pg 46). Examples 11, 12, 14 and 15 describe art-appreciated techniques for antisense suppression, gene therapy and transgenic animals. Example 13 describes kits that could be used in the claimed methods. Example 16 describes that "applicants have identified four leukemias in which cytogenetic banding analyses reveal translocation breakpoints in the PDGFRA gene (chromosome band 4q12) region, and in which - based on cytogenetic correlates - the putative PDGFRA fusion gene is not expected to be BCR" (pg 54). The specificaiton does not clarify how these fusion protein correspond to the claimed methods; i.e., do these fusion proteins have the activating mutations recited in the claims?

The specification teaches that the claimed method is useful for distinguishing between different types of GIST tumors, because "treatment results with imatinib mesylate are significantly better for tumors with evidence of mutational activation of KIT [receptor tyrosine kinase] than for tumors with no KIT mutation" and "testing of clinical specimens for genomic mutations resulting in tyrosine kinase activation will be useful in determining which patients are most likely to respond to a tyrosine kinase inhibitor" [¶ 6]. Heinrich et al (2003; cited above) teaches that "activating mutations in KIT or PDGFRA are mutually exclusive oncogenic events in GISTs and that these mutations have similar biological consequences" (pg 710).

The scope of the claims is as follows. Claims 63, 64 and 67-78 encompass a method of detecting any "biological condition" associated with the recited mutations. Claims 65 and 66 limit the method to "detecting neoplasia" (claim 65) and "wherein the neoplasia comprises a GIST" (claim 66). The specification does not provide a limiting definition of the term "biological condition" and instead only provides examples of such conditions, including a neoplasia that comprises a gastrointestinal stromal tumor (GIST). The specification further implies that any "neoplastic disease such as cancer" (pg 18) or "tumorous growth" (pg 34) is encompassed by the term "biological condition". Thus, the term "biological condition" broadly encompasses any form of biological condition, including any type of disease, disorder or other condition, including vastly disparate disease such as heart disease. Even with the subgenus of "neoplasia" (abnormal cell growth), the claims encompass a broad genus including any form of cancer or tumor. However, the specification provides no guidance as to biological conditions, other than GIST, that are associated with the recited mutations. Instead, the specification merely invites the skilled artisan to investigate other conditions, including other neoplastic diseases, to determine if any of them are associated with the recited mutations. Such investigation would constitute undue experimentation in view of the large genus of encompassed diseases and the lack of guidance as to where the mutations may be found (other than in GISTs). Furthermore, as currently written, claim 1 includes variant sequences shown at any of positions 2072 through 2937 of SEQ ID NO: 26 (865 residues), whereas the specification only teaches mutations in GISTs in residues 2072-2087, 2090-2107 and 2916-2937.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how the claimed method could be used to detect a genus of "biological conditions" associated with an activating mutation in PDGFRA. There are no examples of a biological condition associated with an activating mutation in PDGFRA other than a small percentage (3-6%) of one particular type of tumor (GIST). Thus the specification fails to teach the skilled artisan how to use the claimed method for detection of biological conditions without resorting to undue experimentation. The specification has

not provided the person of ordinary skill in the art the guidance necessary to be able to use the claimed method for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the activating mutations in PDGFRA are associated with other biological conditions, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71-74 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 71 recites the limitation "the PDGFRA molecule" in line 1. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 71 depends from claim 63 and recites "wherein the PDGFRA molecule is a PDGFRA encoding nucleic acid sequence". However, parent claim 63 does not recite the term "PDGFRA molecule".

Claim 73 recites the limitation "the agent" in line 1. There is insufficient antecedent basis for this limitation in the claim. Specifically, claim 73 depends from claim 71 and recites "wherein the agent comprises a labeled nucleotide probe". However, neither of parent claims 63 and 71 recite the term "agent".

Claim 78 recites "...wherein at least one oligonucleotide primer comprises a sequence as represented by at least 15 contiguous nucleotides shown in position(s) 2919 of SEQ ID NO: 3, 2917 and 2918 of SEQ ID NO: ..." The meaning of this limitation is indefinite. It is unclear how "at least 15 contiguous nucleotides" can be shown in a

single position (e.g., 2919 of SEQ ID NO: 3). Thus, the Examiner cannot determine what sequence is comprised by the primer.

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646